

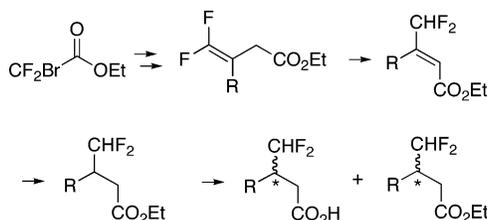
## Stereocontrolled Synthesis of $\beta$ -Difluoromethylated Materials

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Investigation of synthetic routes for regio- and stereocontrolled fluorinated materials with a difluoromethyl group, using ethyl bromodifluoroacetate as a starting material, is described. In particular, (*E*)-difluoromethylated trisubstituted olefins were prepared via the proton migration reaction catalyzed by using fluoride anion. Further, optically active  $\beta$ -difluoromethyl esters were obtained by the enzymatic resolution.

One objective of research in fluorine chemistry, required to support applications in the synthesis of F-analogues of bioactive materials, is the development of methodology and/or reagents suitable for synthesis of all isomers with enantiomeric, diastereomeric, and geometric relationships with unusual selectivity and control.<sup>1</sup> In particular, fluorine-containing molecules with high optical purities have been recognized as a relatively important class of materials because of their interesting characteristics and potential applicability to functionalized materials.<sup>1–3</sup> Recent investigations in this field have opened up the possibility for the introduction of chirality at a carbon bearing a fluoromethyl group and also at the

$\beta$ -position of the functional group,<sup>2</sup> so that the stereoselective synthesis of geometrical isomers with fluorines can be achieved.<sup>2</sup> Until now, the synthetic routes to optically active materials bearing a trifluoromethyl group have been reported.<sup>3</sup> However, synthetic strategies for the stereocontrolled synthesis of difluoromethylated materials have not been studied in detail.<sup>4</sup> Furthermore, the highly geometrically controlled syntheses of trisubstituted alkenes with a fluoromethyl group are not known in the fields examining Hörner–Wadsworth–Emmons reactions and Wittig reactions.<sup>1–3</sup> In contrast, it is known that difluoromethylated materials have been prepared from terminal difluoroolefins by hydrogenation, using a 10% palladium on carbon catalyst<sup>5</sup> or BrF<sub>3</sub>,<sup>6</sup> and their reactions in radical addition,<sup>7</sup> electrophilic cyclizations,<sup>8</sup> and Claisen rearrangement,<sup>9</sup> for the synthesis of difluoromethylene-containing compounds, have been reported. To date, synthetic strategies for the preparation of terminal difluoroolefins have been based on a few methods: (1) the lithiation of 1,1-difluoroethene and trapping

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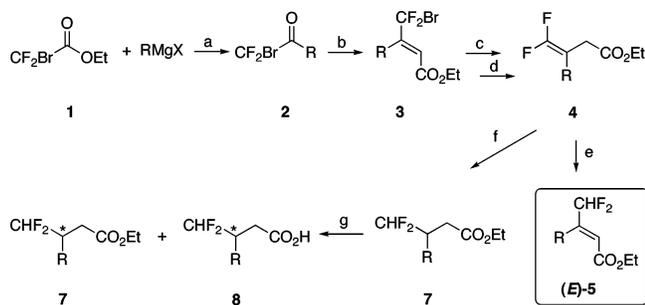
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SCHEME 1<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) Et<sub>2</sub>O, -78 °C, 4 h; (b) (EtO)<sub>2</sub>P(O)-CH<sub>2</sub>CO<sub>2</sub>Et, NaH, THF, -78 °C, 3 h; (c) Zn, DMF, MS 4A; (d) H<sub>2</sub>O; (e) TBAF, DMF; (f) Pd-C, H<sub>2</sub>; (g) Novozym 435, organic solvent.

of the intermediate with CO<sub>2</sub>,<sup>10</sup> (2) the decarboxylation of bromodifluoromethylated malonate,<sup>11</sup> (3) the dehydrofluorination of trifluorinated isobutyrate,<sup>12</sup> and (4) the Wittig difluoromethylation of pyruvate.<sup>13</sup> Moreover, the chemistry of terminal difluoroolefins, which do not undergo elimination to form fluoroolefins, has not been studied for the construction of regio- and stereocontrolled fluorinated materials,<sup>14–17</sup> except for indium-mediated allylation.<sup>18</sup> Clearly, development of selective and/or specific synthetic methods for geometrical isomers and/or optically active  $\beta$ -difluoromethyl esters and/or acids remains an important synthetic challenge.

Accordingly, we have devoted our attention to the development of simple and stereocontrolled synthetic methods for the preparation of a variety of functionalized compounds bearing a difluoromethyl group.

## Results and Discussion

**(E)-Ethyl 3-Substituted 4,4-Difluoro-2-butenate.**

Synthetic intermediates for the (*E*)-ethyl 3-substituted 4,4-difluoro-2-butenates **5** are the terminal difluoroolefins **4** derived from ethyl 3-substituted 4-bromo-4,4-difluoro-2-butenate **3**, which was prepared selectively by the Hörner–Wadsworth–Emmons reaction of ketones **2** in NaH–THF at -78 °C for 3 h. Compounds **3** were purified by column chromatography on silica gel, using a mixture of hexanes–ethyl acetate. The stereochemistry of products **3** was confirmed by <sup>1</sup>H and <sup>19</sup>F NMR coupling constants and chemical shifts. Target terminal difluoroolefins **4** were obtained from the reaction of ethyl 3-substituted 4-bromo-4,4-difluoro-3-butenates **3** with

TABLE 1. Preparation of Ketone 2

compd. no	R	yield (%)
<b>2a</b>	Ph	92
<b>2b</b>	PhCH <sub>2</sub> CH <sub>2</sub>	73
<b>2c</b>	C <sub>5</sub> H <sub>11</sub>	75
<b>2d</b>	C <sub>6</sub> H <sub>13</sub>	56
<b>2e</b>	C <sub>8</sub> H <sub>17</sub>	60

TABLE 2. Preparation of Olefin 3

compd. no	R	yield (%)	<i>E/Z</i> ratio
<b>3a</b>	Ph	85	95:5
<b>3b</b>	PhCH <sub>2</sub> CH <sub>2</sub>	84	95:5
<b>3c</b>	C <sub>5</sub> H <sub>11</sub>	86	94:6
<b>3d</b>	C <sub>6</sub> H <sub>13</sub>	84	94:6
<b>3e</b>	C <sub>8</sub> H <sub>17</sub>	88	94:6

TABLE 3. Preparation of Olefin 4

compd. no	R	yield (%)
<b>4a</b>	Ph	96
<b>4b</b>	PhCH <sub>2</sub> CH <sub>2</sub>	99
<b>4c</b>	C <sub>5</sub> H <sub>11</sub>	85
<b>4d</b>	C <sub>6</sub> H <sub>13</sub>	80
<b>4e</b>	C <sub>8</sub> H <sub>17</sub>	93

TABLE 4. Preparation of Olefin 5

compd. no	R	R <sub>1</sub>	yield (%)	5/6 ratio
<b>5a</b>	Ph		72 (72) <sup>a</sup>	>99:<1 (>99:<1)
<b>5b</b>	PhCH <sub>2</sub> CH <sub>2</sub>	PhCH <sub>2</sub>	85 (63)	>99:<1 (80:20) <sup>a</sup>
<b>5c</b>	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	65 (55)	>99:<1 (83:17)
<b>5d</b>	<i>n</i> -C <sub>6</sub> H <sub>13</sub>	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	75 (62)	>99:<1 (89:11)
<b>5e</b>	<i>n</i> -C <sub>8</sub> H <sub>17</sub>	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	76 (71)	>99:<1 (83:17)

<sup>a</sup> Values in parentheses were the results at room temperature.

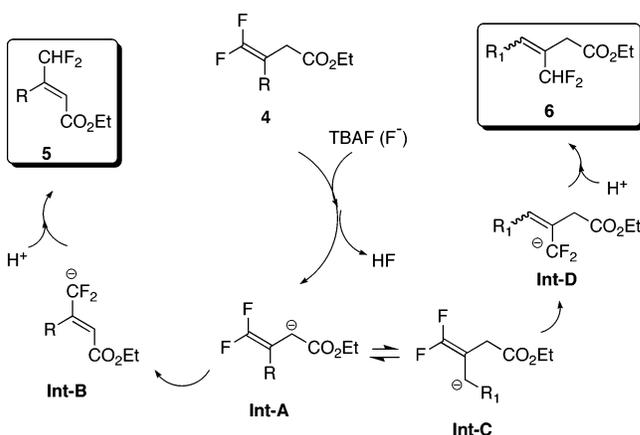


FIGURE 1. Reaction mechanism for the present reaction.

zinc powder in DMF. The yields of terminal difluoroolefins **4** were greatly enhanced by using molecular sieves to decrease the water content in DMF. Highly regio- (>99:<1) and stereoselective syntheses (>99:<1) of (*E*)-ethyl 3-substituted 4,4-difluoro-2-butenate **5** have been achieved via the proton migration reaction of ethyl 3-substituted 4,4-difluoro-3-butenate in the system DMF–fluoride ion [tetra-*n*-butylammonium fluoride (TBAF)] at 12–14 °C. Moreover, we have found that the control of reaction temperature is the most important factor in obtaining the target materials based on the results of detailed examination of the various types of reaction conditions (such as KF–DMF and/or high tem-

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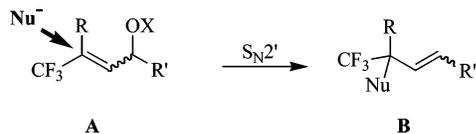
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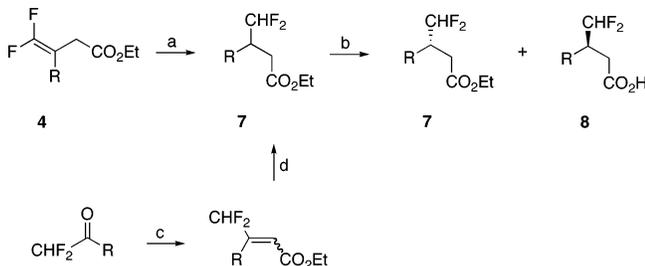
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**FIGURE 2.** Sterecontrolled reaction.

**SCHEME 2<sup>a</sup>**



<sup>a</sup> Reagents and conditions: (a) Pd–C/H<sub>2</sub>: **7** (yield %): R = Ph (80), PhCH<sub>2</sub>CH<sub>2</sub> (67), C<sub>6</sub>H<sub>11</sub> (59), C<sub>6</sub>H<sub>13</sub> (67), C<sub>8</sub>H<sub>17</sub> (65). (b) Novozym (*Candida antarctica*). (c) (EtO)<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>Et, NaH (d) Pd–C/H<sub>2</sub>.

perature, freshly distilled DMF, etc.). In the above migration, when the reaction temperature was kept at 60 °C, the regioselectivity of compounds (*E*)-**5** and **6** decreased to the results shown in Table 4, and the reaction did not proceed quickly below 10 °C. Therefore, it is necessary to keep the reaction temperature at 12–14 °C for a highly regio- and stereoselective synthesis (>99:<1). From these experimental results, the mechanism of the above reaction to give (*E*)-**5** and/or compound **6** is explained as follows. Fluoride anion released from TBAF abstracts the proton on the methylene group, resulting in the formation of intermediates **Int-A**. The generation of **Int-B** from **Int-A** is the major route to afford (*E*)-**5** under kinetic control. The minor route to produce the product **6** is the proton migration, generating the **Int-C** from **Int-A** to give **Int-D** at high temperature under thermodynamic control. The structure of compound **6** (R<sub>1</sub> = PhCH<sub>2</sub>) was determined by NMR spectral data.

**Optically Active Difluoromethylated Materials.**

Recently, we have reported the convenient construction of chiral type **B** molecules with a trifluoromethyl group by the S<sub>N</sub>2' reaction of the corresponding chiral allylic derivatives **A** (Figure 2).<sup>19</sup>

However, in the case of difluoromethylated materials, it is impossible for the stereocontrolled S<sub>N</sub>2' reaction to proceed as far as we examined. For the purpose of constructing chiral type **B** molecules with a difluoromethyl group, we designed the following synthetic strategy. At first, we examined the reduction of (*E*)-ethyl 3-substituted 3-difluoromethylpropenoates to obtain optically active β-difluoromethyl acids and/or esters with the (Rh)-catalyst/H<sub>2</sub> system under pressure. The asymmetric reduction of the compound **5a** (R = Ph) with the Rh-(OCOME)<sub>2</sub>[(*R*)-BINAP]/H<sub>2</sub> system at room temperature for 1 day produces chiral compound **7a** (16% ee) in 30% conversion yield, while compound **5b** (R = PhCH<sub>2</sub>CH<sub>2</sub>) afforded chiral compound **7b** (5% ee in 52% conversion). In the above asymmetric reduction, there are numerous disadvantages associated with the above approach; e.g.,

the optical purity is not high enough to use the precursors for the preparation of highly optically active difluoromethylated materials, the asymmetric catalyst is not practical for the large-scale synthesis, and the reaction time is too long. To obviate these disadvantages, we have developed a second route based upon the kinetic resolution of the corresponding β-difluoromethyl esters with a wide variety of lipases in water and/or organic media.

The results shown in Table 5 support that products would be obtained with high enantioselectivity by controlling the extent of hydrolysis conversion. The asymmetric hydrolysis of the ester *rac*-**7a** (R = Ph) with Novozym 435 (8 × 10<sup>3</sup> unit/mol; *Candida antarctica*, Novo Nordisk Co., Ltd.) afforded 88% ee of optically active ester **7a** at 66% conversion. To obtain **7a** with >95% ee, the recovered ester **7a** needs to be hydrolyzed with Novozym 435. In contrast, lipase QL (*Alcaligenes*, Meito Sangyo Co. Ltd.) produces the corresponding chiral ester **7a** (R = Ph; 97% ee) at 46% conversion.

In conclusion, it has been demonstrated that the above-mentioned synthetic methods are the efficient ways for stereoselectively constructing trisubstituted olefins bearing a difluoromethyl group and optically active β-difluoromethyl esters and/or acids.

**Experimental Section**

**General Procedure.** All commercially available reagents were used without further purification. Chemical shifts of <sup>1</sup>H (300 MHz) and <sup>13</sup>C NMR (75 MHz) spectra were recorded in ppm (δ) downfield from the following internal standard (Me<sub>4</sub>Si, δ 0.00) in CDCl<sub>3</sub>. The <sup>19</sup>F (282 MHz) NMR spectra were recorded in ppm downfield from internal standard C<sub>6</sub>F<sub>6</sub> in CDCl<sub>3</sub> with a VXR 300 instrument.

**General Procedure of the Grignard Reaction To Obtain Bromodifluoromethylated Ketones 2. Bromodifluoromethyl phenyl ketone 2a:** To a mixture of ethyl bromodifluoroacetate (10.2 g, 50 mmol) and diethyl ether (50 mL) was added a solution of phenylmagnesium bromide in diethyl ether (3.0 M, 18.3 mL, 55 mmol) at –78 °C under an argon atmosphere. After the solution was stirred at that temperature for 3 h, the mixture was quenched with 3 N HCl and then extracted with diethyl ether. The extract was dried over anhydrous MgSO<sub>4</sub>, and the solvent was removed. Flash chromatography (silica gel, hexanes–ethyl acetate) afforded compound **2a** in 92% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.52–8.18 (Ar–H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 113.5 (t, *J* = 318 Hz), 128.7, 130.5 (t, *J* = 2.57 Hz), 134.9, 181.0 (t, *J* = 25.8 Hz). <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ 104 ppm from internal C<sub>6</sub>F<sub>6</sub>.

**(*E*)-Ethyl 4-bromo-4,4-difluoro-3-phenyl-2-butenolate 3a:** A mixture of triethyl 2-phosphonoacetate (7.37 g, 15 mmol), bromodifluoromethyl phenyl ketone **2a** (2.35 g, 10 mmol), and NaH (360 mg, 15 mmol) in THF was stirred at 0 °C for 1 h under an argon atmosphere. After the solution was stirred for 2 h at room temperature, it was quenched with aq NH<sub>4</sub>Cl. Oily materials were extracted with diethyl ether, and the extract was dried over MgSO<sub>4</sub>. On removal of the solvent, the resultant crude product was purified by column chromatography on silica gel, using a mixture of hexane and ethyl acetate, in 85% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.04 (3 H, t, *J* = 7.14 Hz), 4.01 (2 H, q), 6.51 (1 H, t, *J* = 1.37 Hz), 7.33–7.43 (Ar–H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 13.6, 60.8, 117.5 (t, *J* = 305 Hz), 121.5 (t, *J* = 7.16 Hz), 127.6, 128.8, 129.2, 131.2, 148.2 (t, *J* = 21.5 Hz), 163.6. <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ 111.2 (d, *J* = 7.63 Hz) ppm from internal C<sub>6</sub>F<sub>6</sub>.

**Ethyl 4,4-difluoro-3-phenyl-3-butenolate 4a:** A mixture of (*E*)-ethyl 4-bromo-4,4-difluoro-3-phenyl-2-butenolate **3a** (305 mg, 1 mmol) and zinc powder (79 mg, 1.2 equiv) in DMF (2 mL) was stirred at room temperature under an argon atmosphere. After the solution was stirred for 4 h at that temper-

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TABLE 5. Asymmetric Hydrolysis with Novozym 435, Lipase PS, or Lipase QL

compd. no	R	time (h)	lipase <sup>a</sup>	conversion <sup>b</sup> (%)	compd <b>7</b> (% ee) <sup>c</sup>	[ $\alpha$ ] <sub>D</sub> (c, CHCl <sub>3</sub> ) <sup>e</sup>
<b>7a</b>	Ph	120	Novozym 435	66	88 (97)	+
		120	lipase PS	77	88 (99)	-42.1 (c, 0.226)
		120	lipase QL	46	97	-
<b>7b</b>	PhCH <sub>2</sub> CH <sub>2</sub>	3	Novozym 435	78	43	+
		120	lipase PS	63	63 (92)	-2.60 (c, 1.062)
		120	lipase QL	68	80	-
<b>7c</b>	C <sub>5</sub> H <sub>11</sub> <sup>d</sup>	3	Novozym 435	69	24	-
		120	lipase PS	61	67 (79)	+
		120	lipase QL	61	65 (89)	+3.10 (c, 1.092)
<b>7d</b>	C <sub>6</sub> H <sub>13</sub> <sup>d</sup>	3	Novozym 435	63	55	-
		120	lipase PS	52	56	+
		120	lipase QL	58	60	+ 2.35 (c, 0.974)
<b>7e</b>	C <sub>8</sub> H <sub>17</sub> <sup>d</sup>	3	Novozym 435	55	52	-
		120	lipase PS	53	58 (88)	+3.16 (c, 1.312)
		120	lipase QL	71	68 (85)	+

<sup>a</sup> Novozym 435 (*Candida antarctica*, Novo Nordisk Co. Ltd.), lipase PS (*Pseudomonas cepacia*, Amano Enzyme Inc.), lipase QL (*Alcaligenes* sp., Meito Sangyo Co. Ltd.). <sup>b</sup> Determined by <sup>19</sup>F NMR. <sup>c</sup> Determined by HPLC analysis (Daicel chiralcel OD or chiralpac AD, *n*-hexane/2-propanol: 99.7/0.3, 1.0 mL/min). % ee in parentheses was obtained from the enzymatic resolution of chiral material derived from the second cycle. <sup>d</sup> Optical purities were determined by HPLC analysis after converting to benzyl esters. <sup>e</sup> [ $\alpha$ ]<sub>D</sub> are the values of % ee in parentheses.

ature, it was quenched with H<sub>2</sub>O. Oily materials were extracted with a mixture of hexanes–ethyl acetate, and the extract was dried over MgSO<sub>4</sub>. On removal of the solvent, the yield was determined by <sup>19</sup>F NMR integral intensities. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.20 (t, *J* = 7.14 Hz), 3.39 (2 H, *J* = 2.2 Hz), 4.12 (2 H, q, *J* = 7.14 Hz), 7.24–7.62 (Ar–H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  13.9, 33.8 (d, *J* = 2.29 Hz), 60.9, 87.1 (m), 127.3, 127.7 (t, *J* = 3.43 Hz), 128.3, 132.8, 154.6 (dd, *J* = 288.6, 288.3 Hz), 169.8. <sup>19</sup>F NMR (CDCl<sub>3</sub>)  $\delta$  72.5 (d, *J* = 35.3 Hz), 73.8 (dt, *J* = 35.3, 2.58 Hz) ppm from internal C<sub>6</sub>F<sub>6</sub>. Anal. Calcd for C<sub>12</sub>H<sub>12</sub>F<sub>2</sub>O<sub>2</sub>: C, 64.01 H; 5.62. Found: C, 63.71; H, 5.35.

**(E)-Ethyl 4,4-difluoro-3-phenyl-2-butenate 5a:** A mixture of ethyl 4,4-difluoro-3-phenyl-3-butenate **4a** (226 mg, 1 mmol) in DMF (2 mL)–fluoride ion [tetra-*n*-butylammonium fluoride (TBAF)] (1.2 equiv, 1.2 mL; 1 M in THF) was stirred at 12–14 °C. After the solution was stirred for 40 min at that temperature, it was quenched with aq NH<sub>4</sub>Cl. Oily materials were extracted with a mixture of hexanes–ethyl acetate, and the extract was dried over MgSO<sub>4</sub>. On removal of the solvent, the resultant crude product was purified by column chromatography on silica gel, using a mixture of hexane and ethyl acetate in 72% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.07 (3 H, *J* = 7.14 Hz), 4.04 (2 H, q, *J* = 7.14 Hz), 6.24 (1 H, td, *J* = 55.2, 0.55 Hz), 6.35 (1 H, t, *J* = 2.20 Hz), 7.24–7.50 (Ar–H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  13.7, 60.7, 114.1 (t, *J* = 242 Hz), 122.8 (t, *J* = 8.88 Hz), 128.1, 128.1, 128.7, 132.3, 146.6 (t, *J* = 20.3 Hz), 164.5. <sup>19</sup>F NMR (CDCl<sub>3</sub>)  $\delta$  45.5 (dd, *J* = 55.2, 2.58 Hz) ppm from internal C<sub>6</sub>F<sub>6</sub>. Anal. Calcd for C<sub>12</sub>H<sub>12</sub>F<sub>2</sub>O<sub>2</sub>: C, 63.54; H, 5.52. Found: C, 63.71; H, 5.35.

**Ethyl 4,4-difluoro-3-phenylbutanoate 7a:** To a MeOH (3.3 mL) solution of ester **4a** (226 mg, 1 mmol) was added 137 mg (0.13 mmol) of 10% Pd/C and the mixture was stirred under hydrogen at 490 kPa pressure for 3 h. On removal of the solvent, the resultant crude product was purified by column chromatography on silica gel, using a mixture of hexane and ethyl acetate, in 80% yield as an oily material. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.15 (3 H, t, *J* = 7.14 Hz), 2.78 (1 H, dd, *J* = 16.2, 9.06 Hz), 2.96 (1 H, dd, *J* = 16.2, 5.77 Hz), 3.55–3.71 (1 H, m), 4.07 (2 H, qd, *J* = 7.14, 2.47 Hz), 5.94 (1 H, td, *J* = 56.6, 3.67 Hz), 7.26–7.38 (Ar–H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  14.0, 33.5 (dd, *J* = 5.15, 3.73 Hz), 45.8 (t, *J* = 20.3 Hz), 60.7, 116.8 (t, *J* = 245 Hz), 127.7, 128.5, 128.5, 135.6, 170.7. <sup>19</sup>F NMR (CDCl<sub>3</sub>)  $\delta$  38.1 (dd, *J* = 278, 18.1 Hz), 42.3 (dd, *J* = 278, 13.8 Hz) ppm from internal C<sub>6</sub>F<sub>6</sub>. IR  $\gamma$  1736 (C=O) cm<sup>-1</sup>. Anal. Calcd for C<sub>12</sub>H<sub>14</sub>F<sub>2</sub>O<sub>2</sub>: C, 63.13; H, 6.21. Found: C, 63.15; H, 6.18.

**Asymmetric Hydrolysis. First cycle:** A mixture of ethyl 4,4-difluoro-3-phenylbutanoate **7a** (114 mg, 0.5 mmol) and Novozym 435 (0.228 g, *Candida antarctica*, Novo Nordisk Co. Ltd.) in phosphate pH 7.4 buffer (1.5 mL) was stirred at room

temperature. After the solution was stirred for 120 h at room temperature, it was filtered over a Celite pad in vacuo. The organic materials were extracted with diethyl ether, and then the extract was dried over anhydrous MgSO<sub>4</sub>. On removal of the solvent, the residues were purified by column chromatography on silica gel, eluting with a mixture of hexanes–ethyl acetate, giving ethyl 4,4-difluoro-3-phenylbutanoate **7a** (88% ee) and 4,4-difluoro-3-phenylbutanoic acid **8a**. Optical purity was determined by HPLC analysis (Daicel Chiralpac AD, *n*-hexane–isopropyl alcohol 99.7:0.3; flow speed 1.0 mL/min; tR (major), 12.6 min; tR (minor), 11.4 min).

**Second cycle:** (a) A mixture of chiral ethyl 4,4-difluoro-3-phenylbutanoate **7a** (70 mg, 0.31 mmol, 88% ee) and Novozym 435 (70 mg) in phosphate pH 7.4 buffer (1 mL) was stirred at room temperature. After the solution was stirred for hours at room temperature, and worked up similar to the above, optically pure ethyl 4,4-difluoro-3-phenylbutanoate **7a** (97% ee) was obtained.

To a solution of ethyl 4,4-difluoro-3-phenylbutanoate **7a** (114 mg, 0.5 mmol) in phosphate buffer (2 mL, pH 7.4) was added lipase QL (171 mg, *Alcaligenes* sp., Meito Sangyo Co. Ltd.) at room temperature. After the solution was stirred for 120 h at room temperature, it was filtered with a Celite pad in vacuo. The solution was diluted with ethyl acetate and then the separated aqueous phase was extracted twice with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub>, and concentrated. The conversion ratio of crude oil was determined by <sup>19</sup>F NMR analysis. The residual was subjected to column chromatography (hexane/ethyl acetate). The optical purity of ethyl 4,4-difluoro-3-phenylbutanoate **7a** (97% ee, 43% yield) was determined by HPLC, using a chiral column (Daicel Chiralpac AD, *n*-hexane–isopropyl alcohol 99.7:0.3; flow speed 1.0 mL/min; tR (major), 11.4 min; tR (minor), 12.6 min).

**4,4-Difluoro-3-phenylbutanoic acid 8a:** <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.81 (1 H, dd, *J* = 16.8, 8.79 Hz), 3.16 (1 H, dd, *J* = 16.8, 5.76 Hz), 3.51–3.67 (1 H, m), 5.91 (1 H, td, *J* = 56.3, 3.30 Hz), 7.26–7.38 (Ar–H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  33.2, 45.5 (t, *J* = 20.3 Hz), 116.7 (t, *J* = 245 Hz), 127.9, 128.5, 128.7, 135.2, 177.3. <sup>19</sup>F NMR (CDCl<sub>3</sub>)  $\delta$  37.7 (ddd, *J* = 278, 56.0, 18.1 Hz), 42.5 (ddd, *J* = 278, 56.0, 13.8 Hz) ppm from internal C<sub>6</sub>F<sub>6</sub>. IR  $\gamma$  1728 (C=O) cm<sup>-1</sup>. Anal. Calcd for C<sub>10</sub>H<sub>10</sub>F<sub>2</sub>O<sub>2</sub>: C, 60.38; H, 5.50. Found: C, 60.00 H, 5.04.

**Supporting Information Available:** NMR spectra for all isolated products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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